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TITLE: Total Synthesis of Eleutherobin and Analogs and Study of
Anti-Cancer Mechanism

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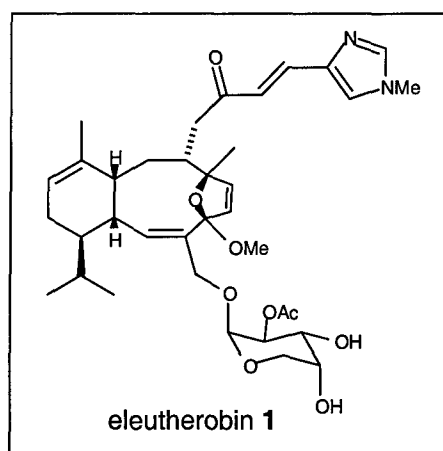
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Table of Contents

Cover.....	
SF 298.....	
Foreword.....	
Table of Contents.....	5
Introduction.....	6
Body.....	7
Key Research Accomplishments.....	9
Reportable Outcomes.....	10
Conclusions.....	11
References.....	12
Appendices.....	N/A

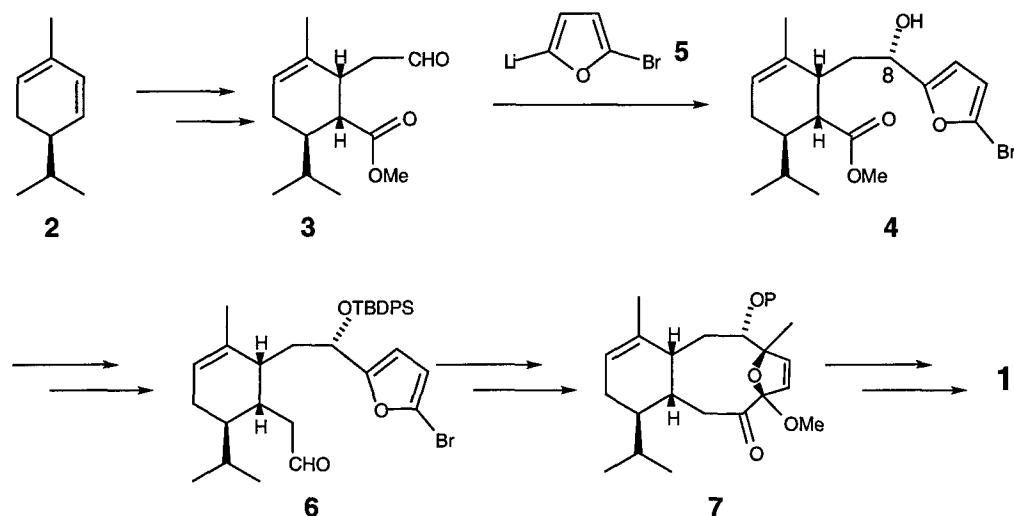
Introduction:

Eleutherobin is a marine natural product discovered in 1994. It serves as one of the most potent anti-cancer agents mimicking Taxol. The proposed research is focused on improving the total synthesis of eleutherobin, and based on that developing eleutherobin analogs for biological studies.



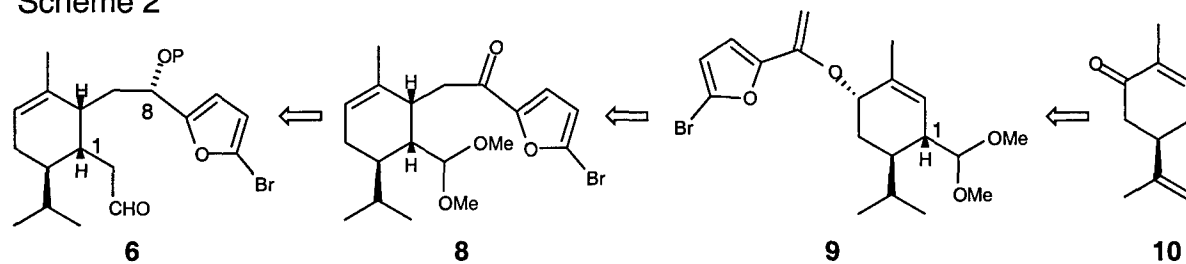
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Scheme 1



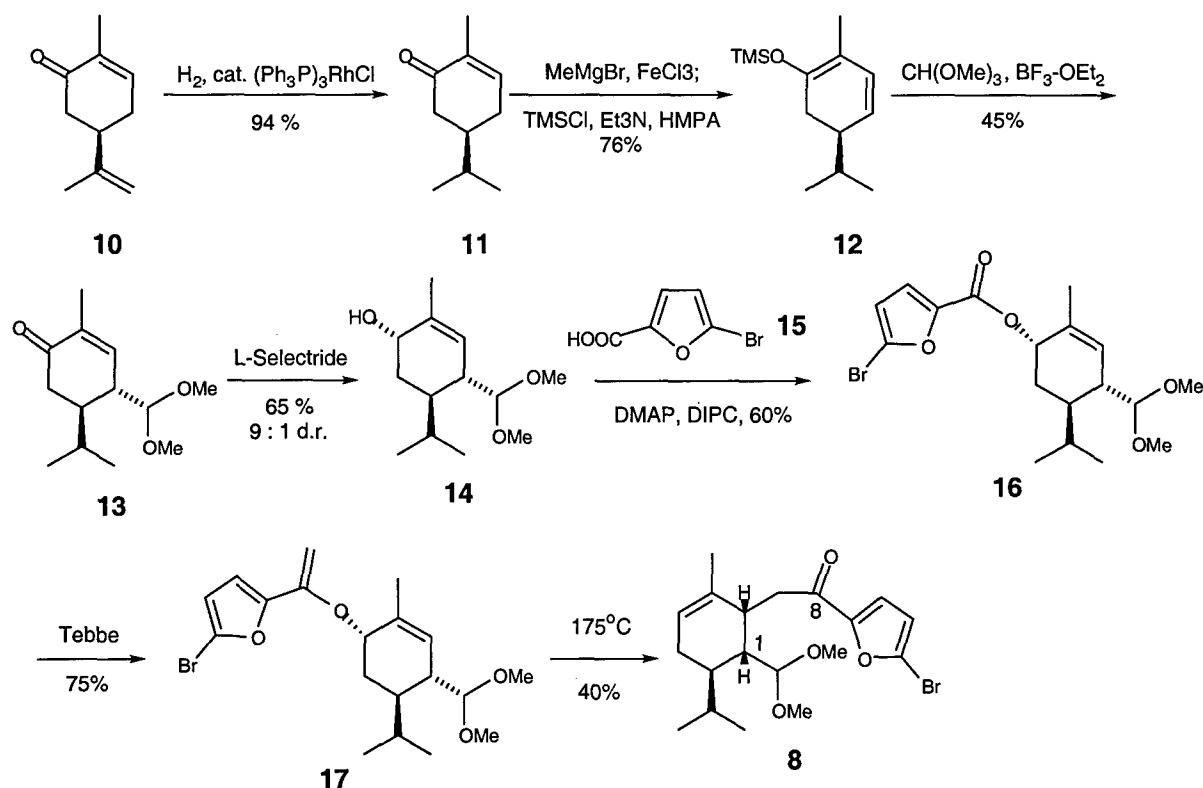
The above Scheme 1 outlines the initial synthesis developed in this lab (1). It features an addition of 2-bromo-5-lithiofuran to aldehyde 3 to give the key intermediate 4 (57% yield). The C8 epimer is also isolated as a minor product (ca. 7:5 diastereomeric ratio). Although the epimer can be recycled, the efficiency of the synthesis certainly has a room for improvement.

Scheme 2



Scheme 2 shows the new retrosynthetic plan in which the key intermediate 6 will be obtained through the reduction of ketone 8. Various reducing agents can be screened to optimize the stereoselectivity. Ketone 8 can be synthesized from 9 through a Claisen rearrangement. Prior to that, the C1 side chain can be installed by alkylation utilizing the enone function of (-)-Carvone 10.

Scheme 3



Scheme 3 shows the current work. The yields are approximate since they are still under optimization. (-)-Carvone **10** was selectively hydrogenated at the terminal double bond using Wilkinson's catalyst without affecting the enone function. As a modification to the reported procedure (2), it was discovered that the application of a moderate high pressure (1600 psi) is necessary for a efficient hydrogenation. The dihydrocarvone **11** obtained was then converted to the thermodynamically more favored TMS ether diene **12**. The published procedure (3) uses a catalytical amount of FeCl_3 , but under our hands a 3.0 eq. of FeCl_3 has to be applied to obtain a satisfactory conversion. Lewis acid induced alkylation leads to dimethyl acetal **13** (4). The stereoselective reduction of the ketone is achieved with L-Selectride (4) to give the alcohol **14**, which was coupled with bromo-furanyl acid **15** to give the ester **16**. Treatment of Tebbe reagent gave **17** which sets up the stage for a Claisen rearrangement to give **8**. Currently, various reducing agents are being tested to reduce C8 ketone to the desired stereoisomer. Work is also being carried out to elongate the C1 side chain by one carbon. Also under study is the idea of installing a two-carbon side chain at C1 in the beginning of the synthesis, which will further shorten the sequence.

Key Research Accomplishments:

Promising results have been obtained on an improved eleutherobin synthesis. Several key steps, including Claisen rearrangement on an advanced intermediate, have been worked out.

Reportable Outcomes:

N/A (early stage of the research).

Conclusions:

An improved eleutherobin synthesis is under development and shows promising results.

Reference:

1. (a) X.-T. Chen, C. E. Gutteridge, S. M. Bhattacharya, B. Zhou, T. P. R. Pettus, T. Hascall, and S. J. Danishefsky *Angew. Chem. Int. Ed.* **1998**, 37, 185-187. (b) X.-T. Chen, B. Zhou, S. M. Bhattacharya, C. E. Gutteridge, , T. P. R. Pettus, and S. J. Danishefsky *Angew. Chem. Int. Ed.* **1998**, 37, 789-792.
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3. O. Takazawa, H. Tamura, K. Kogami, and K. Hayashi *Bull. Chem. Soc. Jpn.*, **1982**, 1907-1911.
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PHYLLIS M. RINEHART
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